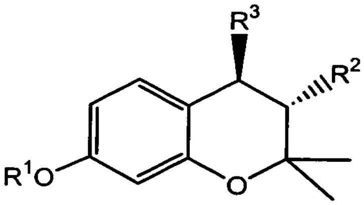
Claims

1. Compounds of the formula I in which substituents R^2 and R^3 are arranged in trans-configuration:



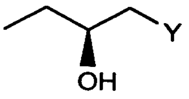
(1)

wherein:

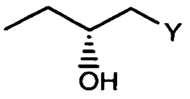
R^1 is H or C1-C6 alkyl; C3-C7 cycloalkyl;

R^2 is phenyl, optionally substituted with 1 to 5 substituents independently selected from the group comprising OH, C1-C6 -alkyl, halogen, nitro, cyano, SH, SR^4, trihalo-C1-C6–alkyl, C1-C6 –alkoxy and phenyl, wherein R^4 is C1-C6 alkyl;

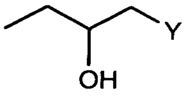
R^3 is phenyl substituted with OR^5 wherein R^5 has the formula (II), (III) or (IV)



(II)



(III)



(IV)

wherein Y is chosen from NHR^4, NR^4_2, $NHCOR^4$, $NHSO_2R^4$, $CONHR^4$, $CONR^4$, $CONR^4_2$, COOH, $COOR^4$, SO_2R^4, SOR^4, $SONHR^4$, $SONR^4_2$, a C3-C7 heterocyclic ring, saturated or unsaturated, containing one or two heteroatoms independently selected from the group consisting of O, S and N, optionally being substituted with 1 to 3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR^4, trihalo-C1-C6– alkyl, C1-C6–alkyl and C1-C6 –alkoxy, preferably NHR^4, NR_2^4, or a nitrogen heterocycle, wherein R^4 is as defined above, and the esters, ethers, and salts of the compounds of formula I, optionally along pharmaceutically acceptable excipients.

2. Compounds as claimed in claim 1, wherein R^3 is phenyl substituted with $-OR^5$ wherein R^5 has the formula II and wherein Y is a C3-C7 heterocyclic ring, saturated or unsaturated, containing one or two heteroatoms independently selected from the group comprising O, S and N, optionally being substituted with 1 to 3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR^4, trihalo-C_1-C_6 – alkyl, C1-C6–alkyl, C1-C6–alkyl and C1-C6–alkoxy.

3. Compounds as claimed in claim 1, wherein R^3 is phenyl substituted with $-OR^5$ wherein R^5 has the formula III and wherein Y is a C3-C7 heterocyclic ring, saturated or unsaturated, containing one or two heteroatoms independently selected from the group comprising O, S and N, optionally being substituted with 1 to 3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR^4, trihalo-C1-C6– alkyl, C1-C6–alkyl, C1-C6–alkyl and C1-C6–alkoxy.

4. Compounds as claimed in claim 1, wherein R^3 is phenyl substituted with $-OR^5$ wherein R^5 has the formula IV and wherein Y is a C3-C7 heterocyclic ring, saturated or unsaturated, containing one or two heteroatoms independently selected from the group comprising O, S and N, optionally being substituted with 1 to 3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR^4, trihalo-C1-C6– alkyl, C1-C6–alkyl, C1-C6–alkyl and C1-C6–alkoxy.

5. Compounds as claimed in claim 1, wherein R^1 is preferably methyl.

6. Compounds as claimed in claim 1, wherein R^2 is preferably phenyl.

7. Compounds as claimed in claim 1, wherein R^4 is preferably butyl.

8. Compounds as claimed in claim 1, wherein the preferred compounds are:
   I. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{2R)-3-methylamino-2-hydroxy}propyloxy] phenyl)-3-phenylchroman.
   II. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{2R)-3-ethylamino-2-hydroxy}propyloxy] phenyl)-3-phenylchroman.
   III. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2R)-3-propylamino-2-hydroxy} propyloxy] phenyl)chroman.
   IV. (3R,4R)-4-(4-[{2R)-3-Butylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman.
   V. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{2R)-3-pentylamino-2-hydroxy}propyloxy] phenyl)-3-phenylchroman.
   VI. (3R,4R)-2,2-Dimethyl-4-(4-[{2R)-3-dimethylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman.
   VII. (3R,4R)-4-(4-[{2R)-3-Diethylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman.
   VIII. (3R,4R)-2,2-Dimethyl-4-(4-[{2R)-3-dipropylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman.
   IX. (3R,4R)-4-(4-[{2R)-3-Dibutylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethoxy-3-phenylchroman.
   X. (3R,4R)-2,2-Dimethyl-4-(4-[{2R)-3-dipentylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman.
   XI. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2R)-3-pyrrolidino-2-hydroxy} propyloxy] phenyl)-chroman.
   XII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2R)-3-piperidino-2-hydroxy} propyloxy]phenyl)-chroman.
   XIII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2R)-3-morpholino-2-hydroxy} propyloxy]phenyl)-chroman.

XIV. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2R)-3-piperazino-2-hydroxy} propyloxy]phenyl)-chroman.

XV. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2R)-3-cyclohexylamino-2-hydroxy} propyloxy]phenyl)-chroman.

XVI. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{2S)-3-methylamino-2-hydroxy}propyloxy] phenyl)-3-phenylchroman.

XVII. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{2S)-3-ethylamino-2-hydroxy} propyloxy]phenyl)-3-phenylchroman.

XVIII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2S)-3-propylamino-2-hydroxy} propyloxy]phenyl)-chroman.

XIX. (3R,4R)-4-4-(4-[{2S)-3-Butylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman.

XX. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{2S)-3-pentylamino-2-hydroxy}propyloxy] phenyl)-3-phenylchroman.

XXI. (3R,4R)-2,2-Dimethyl-4-(4-[{2S)-3-dimethylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman.

XXII. (3R,4R)-4-(4-[{2S)-3-Diethylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman.

XXIII. (3R,4R)-2,2-Dimethyl-4-(4-[{2S)-3-dipropylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman.

XXIV. (3R,4R)-4-(4-[{2S)-3-Dibutylamino-2-hydroxy}propyloxy]phenyl)-3-phenyl)-2,2-dimethoxy-3-phenylchroman.

XXV. (3R,4R)-2,2-Dimethyl-4-(4-[{2S)-3-dipentylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy-3-phenylchroman.

XXVI. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2S)-3-pyrrolidino-2-hydroxy} propyloxy]phenyl)-chroman.

XXVII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2S)-3-piperidino-2-hydroxy} propyloxy]phenyl)-chroman.

XXVIII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2S)-3-morpholoino-2-hydroxy} propyloxy]phenyl)-chroman.

XXIX. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2S)-3-piperazino-2-hydroxy} propyloxy]phenyl)-chroman.

XXX. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{2S)-3-cyclohexylamino-2-hydroxy} propyloxy]phenyl)-chroman.

XXXI. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{3-methylamino-2-hydroxy}propyloxy] phenyl)- 3-phenylchroman.

XXXII. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{3-ethylamino-2-hydroxy}propyloxy]phenyl)-3-phenylchroman.

XXXIII. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{3-propylamino-2-hydroxy}propyloxy]phenyl)-3-phenylchroman.

XXXIV. (3R,4R)-4-(4-[{3-butylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman.

XXXV. (3R,4R)-2,2-Dimethyl-7-methoxy-4-(4-[{3-pentylamino-2-hydroxy}propyloxy]phenyl)-3-phenylchroman.

XXXVI. (3R,4R)-2,2-Dimethyl-4-(4-[{3-dimethylamino-2-hydroxy}propyloxy]phenyl)-7-methoxy phenyl)-3-phenylchroman.

XXXVII. (3R,4R)-4-(4-[{3-Diethylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethyl-7-methoxy-3-phenylchroman.

XXXVIII. (3R,4R)-2,2-Dimethyl-4-(4-[{3-dipropylamino-2-hydroxy}propyloxy]phenyl-7-methoxy phenyl)-3-phenylchroman.

XXXIX. (3R,4R)-4-(4-[{3-Dibutylamino-2-hydroxy}propyloxy]phenyl)-2,2-dimethoxy-3-phenylchroman.

XL. (3R,4R)-2,2-Dimethyl-4-(4-[{3-dipentylamino-2-hydroxy}propyloxy]phenyl-7-methoxy phenyl)-3-phenylchroman.

XLI. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{3-pyrrolidino-2-hydroxy}propyloxy] phenyl)-chroman.

XLII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{3-piperidino-2-hydroxy}propyloxy] phenyl)-chroman.

XLIII. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{3-morpholino-2-hydroxy}propyloxy] phenyl)-chroman.

XLIV. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{3-piperazino-2-hydroxy}propyloxy] phenyl)-chroman.

XLV. (3R,4R)-2,2-Dimethyl-7-methoxy-3-phenyl-4-(4-[{3-cyclohexylamino-2-hydroxy} propyloxy]phenyl)-chroman.

9. Compounds as claimed in claim 1, wherein the salts are selected from a group comprising acid addition salts consisting of formate, acetate, phenyl acetate, trifluroacetate, acrylate, ascorbate, benzoate, chlorobenzoates, bromobezoates, iodobenzoates, nitrobenzoates, hydroxybenzoates, alkylbenzoates, alkyloxybenzoates, alkoxycarbonylbenzoates, naphthalene-2 benzoate, butyrates, phenylbutyrates, hydroxybutyrates, caprate, caprylate, cinnamate, mandelate, mesylate, citrate, tartarate, fumarate, heptanoate, hippurate, lactate, malate, maleate, malonate, nicotinate, isonicotinate, oxalate, phthalate, terephthalate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacte, succinate, suberate, sulphate, bisulphate, pyrosulphate, sulphite, bisulphate, sulphonate, benzene sulphonate, bromobenzene sulphonates, chlorobenzene sulphonates, ethane sulphonates, methane sulphonates, naphthalene sulphonates, toluene sulphonates, and the likes.

10. Compounds as claimed in claim 1, wherein most preferred salts are methyl iodide, fumerate, ascorbate, and hydrochloride.

11. Compounds as claimed in claim 1, wherein the compounds or its salts are in the physical forms of the gelatin capsules or compressed into the tablets or pills or may be formulated in the form of lozenges, inclusion complexes with cyclodextrin derivatives, injectable depo formulations, aerosols, granules, powders, oral liquids, mucosal adhesive formulations, gel formulations, troches, elixirs, suspensions, syrups, wafers, liposomal delivery systems, implants, suppository, pessary, microemulsions, nanoemulsion, microparticles, nanoparticles, controlled release delivery systems, transdermal delivery systems,

and targeted delivery systems such as conjugates with monoclonal antibodies or with other suitable carrier moieties.

12. Compounds as claimed in claim 1, wherein the pharmaceutically acceptable excipients are selected from a group comprising:

a) diluent such as lactose, mannitol, sorbitol, microcrystalline cellulose, sucrose, sodium citrate, dicalcium phosphate, or any other ingredient of the similar nature alone or in a suitable combination thereof;

b) a binder such as gum tragacanth, gum acacia, methyl cellulose, gelatin, polyvinyl pyrrolidone, starch or any other ingredient of the similar nature alone or in a suitable combination thereof;

c) a disintegrating agent such as agar-agar, calcium carbonate, sodium carbonate, silicates, alginic acid, corn starch, potato tapioca starch, primogel or any other ingredient of the similar nature alone or in a suitable combination thereof;

d) a lubricant such as magnesium stearate, calcium stearate or steorotes, talc, solid polyethylene glycols, sodium lauryl sulphate or any other ingredient of the similar nature alone or in a suitable combination thereof;

e) a glidant such as colloidal silicon dioxide or any other ingredient of the similar nature alone or in a suitable combination thereof;

f) a sweetening agent such as sucrose, saccharin or any other ingredient of the similar nature alone or in a suitable combination thereof;

g) a flavoring agent such as peppermint, methyl salicylate, orange flavor, vanilla flavor, or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof;

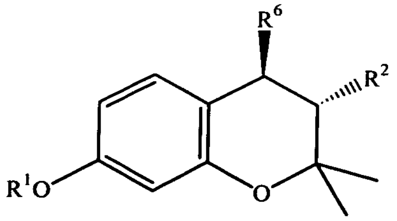
h) a wetting agents such as cetyl alcohol, glyceryl monostearate or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof;

i) a absorbents such as kaolin, bentonite clay or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof; and

j) a solution retarding agents such as wax, paraffin or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof.

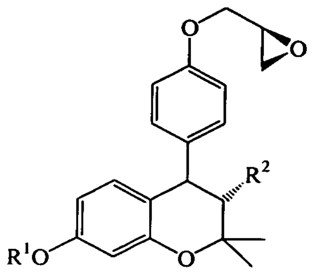
13. A process for the preparation of compounds of formula I, said process comprising steps of:

I. reacting a compound of formula V in which substituents R^2 and R^6 are arranged in the (3R,4R) configuration: wherein R^1 and R^2 are as defined in formula 1 and R^6 is phenyl substituted with a hydroxy substituents at C2, C3 or C4, preferably at C4 with a compound of formula VI, VII, VIII, neat or in an aprotic solvent which includes dimethylsulphoxide, dimethylformamide in the presence of a base such as K_2CO_3 at temperature ranging between 50 to 120^0C,

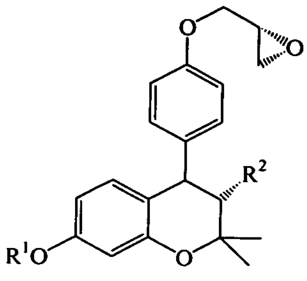


(V)

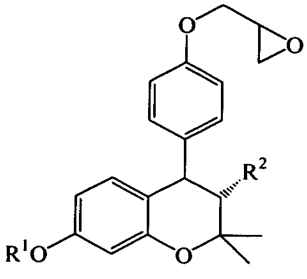
II. obtaining compounds of structure IX (a-c) wherein R^1 and R^2 are as defined in formula 1,



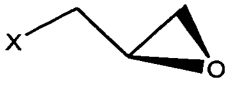
(IX a)



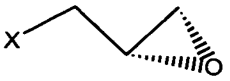
(IXb)



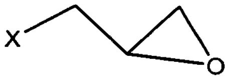
(IXc)



(VI)
R



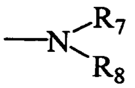
(VII)
S



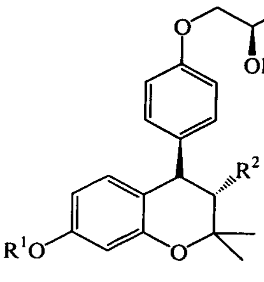
(VIII)
R,S

III. reacting compound of formula IX a-c with a nucleophile preferably an amine of formula X wherein R^7 and R^8 are individually hydrogen, C1-C6-alkyl which includes straight chain as well as branched alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl C1-C6-cycloalkyl which includes cyclopropane, cyclobutane, cyclopentane, cyclohexane or form a C3-C7 heterocyclic ring, saturated or unsaturated, containing one or two heteroatoms independently selected from the group comprising O, S and N, optionally being substituted with 1,2,3 substituents independently selected from the group comprising H, OH, halogen, nitro, cyano, SH, SR^4, trihalo-C1-C6-alkyl, C1-C6-alkyl and C1-C6-alkoxy, wherein R^4 is defined above, either neat or in the presence of organic solvent such as benzene, dimethylsulphoxide, dimethylformamide, and

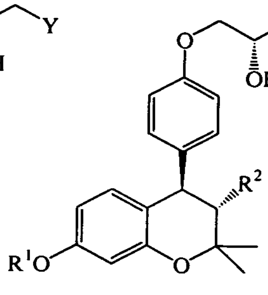
IV. obtaining compounds of formula XI a-c, optionally converting the amino derivative into their corresponding salts such as HCL, fumerate, citrate by treating the free base with the corresponding acid.



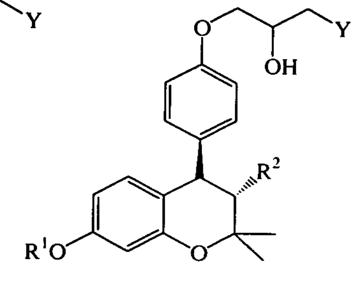
(X)



(XI a)



(XI b)



(XI c)

wherein Y, R^1 and R^2 are as defined above.

14. A method of preventing and/or treating estrogen-related disease conditions in a subject in need thereof, said method comprising step of administering to the subject, a pharmaceutically effective amount of compounds of formula 1, or its salts, optionally along with pharmaceutically acceptable excipients.

15. A method of treatment as claimed in claim 14, wherein the salts are selected from a group comprising acid addition salts consisting of formate, acetate, phenyl acetate, trifluroacetate, acrylate, ascorbate, benzoate, chlorobenzoates, bromobezoates, iodobenzoates, nitrobenzoates, hydroxybenzoates, alkylbenzoates, alkyloxybenzoates, alkoxycarbonylbenzoates, naphthalene-2 benzoate, butyrates, phenylbutyrates, hydroxybutyrates, caprate, caprylate, cinnamate, mandelate, mesylate, citrate, tartarate, fumarate, heptanoate, hippurate, lactate, malate, maleate, malonate, nicotinate, isonicotinate, oxalate, phthalate, terephthalate, phosphate, monohydrogen phosphate, dihydrogen phosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate,

salicylate, sebacte, succinate, suberate, sulphate, bisulphate, pyrosulphate, sulphite, bisulphate, sulphonate, benzene sulphonate, bromobenzene sulphonates, chlorobenzene sulphonates, ethane sulphonates, methane sulphonates, naphthalene sulphonates, toluene sulphonates, and alkyl or aryl halides addtion salts of the compounds of this invention, wherein the alkyl halide is selected from a group comprising C_1 to C_{18} alkyl halide, and aryl halide is selected from a group comprising benzyl halide and substituted benzyl halide.

16. A method of treatment as claimed in claim 14, wherein most preferred salts are methyl iodide, fumerate, ascorbate, and hydrochloride.

17. A method of treatment as claimed in claim 14, wherein the administration is through various routes selected from a group comprising oral, systemic, local, and topical delivery selected from a group consisting of intravenous, intra-arterial, intra-muscular, subcutaneous, intra-peritoneal, intra-dermal, buccal, intranasal, inhalation, vaginal, rectal, and transdermal.

18. A method of treatment as claimed in claim 14, wherein the preferred route of administration is oral route.

19. A method of treatment as claimed in claim 14, wherein the physical forms of the compound of formula 1 and its salts could be gelatin capsules or compressed into the tablets or pills or may be formulated in the form of lozenges, inclusion complexes with cyclodextrin derivatives, injectable depo formulations, aerosols, granules, powders, oral liquids, mucosal adhesive formulations, gel formulations, troches, elixirs, suspensions, syrups, wafers, liposomal delivery systems, implants, suppository, pessary, microemulsions, nanoemulsion, microparticles, nanoparticles, controlled release delivery systems, transdermal delivery systems, and targeted delivery systems such as conjugates with monoclonal antibodies or with other suitable carrier moieties.

20. A method of treatment as claimed in claim 14, wherein the pharmaceutically acceptable excipients are selected from a group comprising:

a) diluent such as lactose, mannitol, sorbitol, microcrystalline cellulose, sucrose, sodium citrate, dicalcium phosphate, or any other ingredient of the similar nature alone or in a suitable combination thereof;

b) a binder such as gum tragacanth, gum acacia, methyl cellulose, gelatin, polyvinyl pyrrolidone, starch or any other ingredient of the similar nature alone or in a suitable combination thereof;

c) a disintegrating agent such as agar-agar, calcium carbonate, sodium carbonate, silicates, alginic acid, corn starch, potato tapioca starch, primogel or any other ingredient of the similar nature alone or in a suitable combination thereof;

d) a lubricant such as magnesium stearate, calcium stearate or steorotes, talc, solid polyethylene glycols, sodium lauryl sulphate or any other ingredient of the similar nature alone or in a suitable combination thereof;

e) a glidant such as colloidal silicon dioxide or any other ingredient of the similar nature alone or in a suitable combination thereof;

f) a sweetening agent such as sucrose, saccharin or any other ingredient of the similar nature alone or in a suitable combination thereof;

g) a flavoring agent such as peppermint, methyl salicylate, orange flavor, vanilla flavor, or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof;

h) a wetting agents such as cetyl alcohol, glyceryl monostearate or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof;

i) an absorbents such as kaolin, bentonite clay or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof; and

j) a solution retarding agents such as wax, paraffin or any other pharmaceutically acceptable flavor alone or in a suitable combination thereof.

21. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in preferably diseases or syndromes caused by an estrogen-deficient state, with Relative Binding affinity (RBA) to estrogen receptors ranging between 5 to 7.

22. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in disease conditions caused by osteoporosis, bone loss, and bone formation, with T/C ratio of ≤ 0.6.

23. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in disease conditions affecting cardiovascular systems, more particularly hyperlipidaemia, thrombosis and vasomotor system.

24. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in disease conditions showing neurodegenerative effects, more particularly, stroke, senile dementia-Alzheimer type and Parkinson disease.

25. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in disease conditions showing menopausal symptoms, more particularly, hot flushes, urogenital atrophy, depression, mania, schizophrenia, urinary incontinence, dysmenorrhea, dysfunctional uterine bleeding, acne, hirsutism, improper ovarian development.

26. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in disease conditions showing cancers, more particularly, prostatic carcinoma, breast cancer, cancer of uterus, cancer of the cervix and colon cancer, with LC_{50} ranging between 17 to 20 μM.

27. A method as claimed in claim 26, wherein the volume of the tumor decreases by about 25%.

28. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps regulate fertility in humans and in other animals.

29. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in threatened or habitual abortion.

30. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in suppression of post-partum lactation.

31. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps in the management of certain physiological disorders, more particularly, obesity and depression.

32. A method of prevention and/or treatment as claimed in claim 14, wherein said method helps regulate of glucose metabolism in non-insulin dependent diabetes mellitus.